

WARNING

Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after many months of treatment. The risk of developing hepatitis is age related. Approximate case rates by age are: 0 per 1,000 for persons under 20 years of age, 3 per 1,000 for persons in the 20–34 year age group, 12 per 1,000 for persons in the 35–49 year age group, 23 per 1,000 for persons in the 50–64 year age group, and 8 per 1,000 for persons over 65 years of age. The risk of hepatitis is increased with daily consumption of alcohol. Precise data to provide a fatality rate for isoniazid-related hepatitis is not available; however, in a U.S. Public Health Service Surveillance Study of 13,838 persons taking isoniazid, there were 8 deaths among 174 cases of hepatitis.

Therefore, patients given isoniazid should be carefully monitored and interviewed at monthly intervals. Serum transaminase concentration becomes elevated in about 10–20 percent of patients, usually during the first few months of therapy, but it can occur at any time. Usually enzyme levels return to normal despite continuance of drug, but in some cases progressive liver dysfunction occurs. Patients should be instructed to report immediately any of the prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea, or vomiting. If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid should be discontinued promptly, since continued use of the drug in these cases has been reported to cause a more severe form of liver damage.

Patients with tuberculosis should be given appropriate treatment with alternative drugs. If isoniazid must be reinstituted, it should be reinstituted only after symptoms and laboratory abnormalities have cleared. The drug should be restarted in very small and gradually increasing doses and should be withdrawn immediately if there is any indication of recurrent liver involvement. Treatment should be deferred in persons with acute hepatic diseases.

DESCRIPTION

RIFAMATE is a combination capsule containing 300 mg rifampin and 150 mg isoniazid. The capsules also contain as inactive ingredients: colloidal silicon dioxide, FD&C Blue No. 1, FD&C Red No. 40, gelatin, magnesium stearate, sodium starch glycolate, and titanium dioxide.

Rifampin is a semisynthetic antibiotic derivative of rifamycin B. The chemical name for rifampin is 3-(4-methyl-1-piperazinyliminomethyl) rifamycin SV.

Isoniazid is the hydrazide of isonicotinic acid. It exists as colorless or white crystals or as a white, crystalline powder that is water soluble, odorless, and slowly affected by exposure to air and light.

CLINICAL PHARMACOLOGY

Rifampin

Rifampin inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme. This is the mechanism of action by which rifampin exerts its therapeutic effect. Rifampin cross-resistance has only been shown with other rifamycins.

In a study of 14 normal human adult males, peak blood levels of rifampin occurred 1 1/2 to 3 hours following oral administration of two RIFAMATE capsules. The peaks ranged from 6.9 to 14 mcg/ml with an average of 10 mcg/ml.

In normal subjects the T_{1/2} (biological half-life) of rifampin in blood is approximately 3 hours. Elimination occurs mainly through the bile and, to a much lesser extent, the urine.

Isoniazid

Isoniazid acts against actively growing tubercle bacilli.

After oral administration isoniazid produces peak blood levels within 1 to 2 hours which decline to 50% or less within 6 hours. It diffuses readily into all body fluids (cerebrospinal, pleural, and ascitic fluids), tissues, organs, and excreta (saliva, sputum, and feces). The drug also passes through the placental barrier and into milk in concentrations comparable to those in the plasma. From 50 to 70% of a dose of isoniazid is excreted in the urine in 24 hours.

Isoniazid is metabolized primarily by acetylation and dehydrazination. The rate of acetylation is genetically determined.

Approximately 50% of Blacks and Caucasians are "slow inactivators"; the majority of Eskimos and Orientals are "rapid inactivators." The rate of acetylation does not significantly alter the effectiveness of isoniazid. However, slow acetylation may lead to higher blood levels of the drug, and thus an increase in toxic reactions.

Pyridoxine deficiency (B₆) is sometimes observed in adults with high doses of isoniazid and is considered probably due to its competition with pyridoxal phosphate for the enzyme apotryptophanase.

INDICATIONS AND USAGE

For pulmonary tuberculosis in which organisms are susceptible, and when the patient has been titrated on the individual components and it has therefore been established that this fixed dosage is therapeutically effective.

This fixed-dosage combination drug is not recommended for initial therapy of tuberculosis or for preventive therapy. In the treatment of tuberculosis, small numbers of resistant cells, present within large populations of susceptible cells, can rapidly become the predominating type. Since rapid emergence of resistance can occur, culture and susceptibility tests should be performed in the event of persistent positive cultures. This drug is not indicated for the treatment of meningococcal infections or asymptomatic carriers of *N. meningitidis* to eliminate meningococci from the nasopharynx.

CONTRAINDICATIONS

Previous isoniazid-associated hepatic injury; severe adverse reactions to isoniazid, such as drug fever, chills, and arthritis; acute liver disease of any etiology. A history of previous hypersensitivity reaction to any of the rifamycins or to isoniazid, including drug-induced hepatitis.

WARNINGS

RIFAMATE (rifampin and isoniazid capsules USP) is a combination of two drugs, each of which has been associated with liver dysfunction. Liver function tests should be performed prior to therapy with RIFAMATE and periodically during treatment.

Rifampin

Rifampin has been shown to produce liver dysfunction. There have been fatalities associated with jaundice in patients with liver disease or receiving rifampin concomitantly with other hepatotoxic agents. Since an increased risk may exist for individuals with liver disease, benefits must be weighed carefully against the risk of further liver damage.

Several studies of tumorigenicity potential have been done in rodents. In one strain of mice known to be particularly susceptible to the spontaneous development of hepatomas, rifampin given at a level 2–10 times the maximum dosage used clinically resulted in a significant increase in the occurrence of hepatomas in female mice of this strain after one year of administration.

There was no evidence of tumorigenicity in the males of this strain, in males or females of another mouse strain, or in rats.

Isoniazid

See the boxed warning.

PRECAUTIONS

Rifampin

Rifampin is not recommended for intermittent therapy; the patient should be cautioned against intentional or accidental interruption of the daily dosage regimen since rare renal hypersensitivity reactions have been reported when therapy was resumed in such cases.

Rifampin has been observed to increase the requirements for anticoagulant drugs of the coumarin type. The cause of the phenomenon is unknown. In patients receiving anticoagulants and rifampin concurrently, it is recommended that the prothrombin time be performed daily or as frequently as necessary to establish and maintain the required dose of anticoagulant.

Urine, feces, saliva, sputum, sweat, and tears may be colored red-orange by rifampin and its metabolites. Soft contact lenses may be permanently stained. Individuals to be treated should be made aware of these possibilities.

It has been reported that the reliability of oral contraceptives may be affected in some patients being treated for tuberculosis with rifampin in combination with at least one other antituberculosis drug. In such cases, alternative contraceptive measures may need to be considered.

It has also been reported that rifampin given in combination with other antituberculosis drugs may decrease the pharmacologic activity of methadone, oral hypoglycemics, digitoxin, quinidine, disopyramide, dapsone, and corticosteroids. In these cases, dosage adjustment of the interacting drugs is recommended.

Therapeutic levels of rifampin have been shown to inhibit standard microbiological assays for serum folate and vitamin B₁₂.

Alternative methods must be considered when determining folate and vitamin B₁₂ concentrations in the presence of rifampin.

Since rifampin has been reported to cross the placental barrier and appear in cord blood and in maternal milk, neonates and newborns of rifampin-treated mothers should be carefully observed for any evidence of untoward effects.

Isoniazid

All drugs should be stopped and an evaluation of the patient should be made at the first sign of a hypersensitivity reaction.

Use of isoniazid should be carefully monitored in the following:

1. Patients who are receiving phenytoin (diphenylhydantoin) concurrently. Isoniazid may decrease the excretion of phenytoin or may enhance its effects. To avoid phenytoin intoxication, appropriate adjustment of the anticonvulsant dose should be made.
2. Daily users of alcohol. Daily ingestion of alcohol may be associated with a higher incidence of isoniazid hepatitis.
3. Patients with current chronic liver disease or severe renal dysfunction.

Periodic ophthalmoscopic examination during isoniazid therapy is recommended when visual symptoms occur.

Usage in Pregnancy and Lactation

Rifampin

Although rifampin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampin, alone or in combination with other antituberculosis drugs, on the human fetus is not known. An increase in congenital malformations, primarily spina bifida and cleft palate, has been reported in the offspring of rodents given oral doses of 150–250 mg/kg/day of rifampin during pregnancy.

The possible teratogenic potential in women capable of bearing children should be carefully weighed against the benefits of therapy.

Isoniazid

It has been reported that in both rats and rabbits, isoniazid may exert an embryocidal effect when administered orally during pregnancy, although no isoniazid-related congenital anomalies have been found in reproduction studies in mammalian species (mice, rats, and rabbits). Isoniazid should be prescribed during pregnancy only when therapeutically necessary. The benefit of preventive therapy should be weighed against a possible risk to the fetus. Preventive treatment generally should be started after delivery because of the increased risk of tuberculosis for new mothers.

Since isoniazid is known to cross the placental barrier and to pass into maternal breast milk, neonates and breast-fed infants of isoniazid-treated mothers should be carefully observed for any evidence of adverse effects.

Carcinogenesis

Isoniazid has been reported to induce pulmonary tumors in a number of strains of mice.

ADVERSE REACTIONS

Rifampin

Nervous system reactions: headache, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, visual disturbances, muscular weakness, pain in extremities, and generalized numbness

Gastrointestinal disturbances: in some patients heartburn, epigastric distress, anorexia, nausea, vomiting, gas, cramps, and diarrhea

Hepatic reactions: transient abnormalities in liver function tests (e.g., elevations in serum bilirubin, BSP, alkaline phosphatase, serum transaminases) have been observed. Rarely, hepatitis or a shocklike syndrome with hepatic involvement and abnormal liver function tests.

Renal reactions: elevations in BUN and serum uric acid have been reported. Rarely, hemolysis, hemoglobinuria, hematuria, interstitial nephritis, renal insufficiency, and acute renal failure have been noted. These are generally considered to be hypersensitivity reactions. They usually occur during intermittent therapy or when treatment is resumed following intentional or accidental interruption of a daily dosage regimen, and are reversible when rifampin is discontinued and appropriate therapy instituted.

Hematologic reactions: thrombocytopenia, leukopenia, hemolytic anemia, eosinophilia, and decreased hemoglobin have been observed. Thrombocytopenia has occurred when rifampin and ethambutol were administered concomitantly according to an intermittent dose schedule twice weekly and in high doses. Agranulocytosis has been reported very rarely.

Allergic and immunological reactions: occasionally pruritus, urticaria, rash, pemphigoid reaction, eosinophilia, sore mouth, sore tongue, and exudative conjunctivitis. Rarely, hemolysis, hemoglobinuria, hematuria, renal insufficiency or acute renal failure have been reported which are generally considered to be hypersensitivity reactions. These have usually occurred during intermittent therapy or when treatment was resumed following intentional or accidental interruption of a daily dosage regimen and were reversible when rifampin was discontinued and appropriate therapy instituted.

Although rifampin has been reported to have an immunosuppressive effect in some animal experiments, available human data indicate that this has no clinical significance.

Metabolic reactions: elevations in BUN and serum uric acid have occurred.

Miscellaneous reactions: fever and menstrual disturbances have been noted.

Isoniazid

The most frequent reactions are those affecting the nervous system and the liver.

Nervous system reactions: peripheral neuropathy is the most common toxic effect. It is dose-related, occurs most often in the malnourished and in those predisposed to neuritis (e.g., alcoholics and diabetics), and is usually preceded by paresthesias of the feet and hands. The incidence is higher in "slow inactivators."

Other neurotoxic effects, which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment, and toxic psychosis.

Gastrointestinal reactions: nausea, vomiting, and epigastric distress

Hepatic reactions: elevated serum transaminases (SGOT; SGPT), bilirubinemia, bilirubinuria, jaundice, and occasionally severe and sometimes fatal hepatitis. The common prodromal symptoms are anorexia, nausea, vomiting, fatigue, malaise, and weakness. Mild and transient elevation of serum transaminase levels occurs in 10 to 20 percent of persons taking isoniazid. The abnormality usually occurs in the first 4 to 6 months of treatment but can occur at any time during therapy. In most instances, enzyme levels return to

normal with no necessity to discontinue medication. In occasional instances, progressive liver damage occurs, with accompanying symptoms. In these cases, the drug should be discontinued immediately. The frequency of progressive liver damage increases with age. It is rare in persons under 20, but occurs in up to 2.3 percent of those over 50 years of age.

Hematologic reactions: agranulocytosis, hemolytic sideroblastic or aplastic anemia, thrombocytopenia, and eosinophilia

Hypersensitivity reactions: fever, skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative), lymphadenopathy, and vasculitis

Metabolic and endocrine reactions: pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis, and gynecomastia

Miscellaneous reactions: rheumatic syndrome and systemic lupus erythematosus-like syndrome

OVERDOSAGE

Rifampin

Signs and Symptoms

Nausea, vomiting, and increasing lethargy will probably occur within a short time after ingestion; actual unconsciousness may occur with severe hepatic involvement. Brownish-red or orange discoloration of the skin, urine, sweat, saliva, tears, and feces is proportional to amount ingested.

Liver enlargement, possibly with tenderness, can develop within a few hours after severe overdosage, and jaundice may develop rapidly. Hepatic involvement may be more marked in patients with prior impairment of hepatic function. Other physical findings remain essentially normal.

Direct and total bilirubin levels may increase rapidly with severe overdosage; hepatic enzyme levels may be affected, especially with prior impairment of hepatic function. A direct effect upon hemopoietic system, electrolyte levels, or acid-base balance is unlikely.

Isoniazid

Signs and Symptoms

Isoniazid overdosage produces signs and symptoms within 30 minutes to 3 hours. Nausea, vomiting, dizziness, slurring of speech, blurring of vision, visual hallucinations (including bright colors and strange designs), are among the early manifestations. With marked overdosage, respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, are to be expected, along with severe, intractable seizures. Severe metabolic acidosis, acetonuria, and hyperglycemia are typical laboratory findings.

RIFAMATE (rifampin and isoniazid capsules USP)

Treatment

The airway should be secured and adequate respiratory exchange established. Only then should gastric emptying (lavage-aspiration) be attempted; this may be difficult because of seizures. Since nausea and vomiting are likely to be present, gastric lavage is probably preferable to induction of emesis.

Activated charcoal slurry instilled into the stomach following evacuation of gastric contents can help absorb any remaining drug in the GI tract. Antiemetic medication may be required to control severe nausea and vomiting.

Blood samples should be obtained for immediate determination of gases, electrolytes, BUN, glucose, etc. Blood should be typed and crossmatched in preparation for possible hemodialysis.

Rapid control of metabolic acidosis is fundamental to management. Intravenous sodium bicarbonate should be given at once and repeated as needed, adjusting subsequent dosage on the basis of laboratory findings (i.e., serum sodium, pH, etc.). At the same time, anticonvulsants should be given intravenously (i.e., barbiturates, diphenylhydantoin, diazepam) as required, and large doses of intravenous pyridoxine.

Forced osmotic diuresis must be started early and should be continued for some hours after clinical improvement to hasten renal clearance of drug and help prevent relapse. Fluid intake and output should be monitored.

Bile drainage may be indicated in presence of serious impairment of hepatic function lasting more than 24–48 hours. Under these circumstances and for severe cases, extracorporeal hemodialysis may be required; if this is not available, peritoneal dialysis can be used along with forced diuresis.

Along with measures based on initial and repeated determination of blood gases and other laboratory tests as needed, meticulous respiratory and other intensive care should be utilized to protect against hypoxia, hypotension, aspiration, pneumonitis, etc.

In patients with previously adequate hepatic function, reversal of liver enlargement and impaired hepatic excretory function probably will be noted within 72 hours, with rapid return toward normal thereafter.

Untreated or inadequately treated cases of gross isoniazid overdosage can terminate fatally, but good response has been reported in most patients brought under adequate treatment within the first few hours after drug ingestion.

DOSAGE AND ADMINISTRATION

In general, therapy should be continued until bacterial conversion and maximal improvement have occurred.

Adults: Two RIFAMATE (rifampin and isoniazid capsules USP) capsules (600 mg rifampin, 300 mg isoniazid) once daily, administered one hour before or two hours after a meal.

Concomitant administration of pyridoxine (B₆) is recommended in the malnourished, in those predisposed to neuropathy (e.g., diabetic), and in adolescents.

Susceptibility Testing

Rifampin

Rifampin susceptibility powders are available for both direct and indirect methods of determining the susceptibility of strains of mycobacteria. The MIC's of susceptible clinical isolates when determined in 7H10 or other non-egg-containing media have ranged from 0.1 to 2 mcg/ml.

Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure has been recommended for use with discs for testing susceptibility to rifampin. Interpretations correlate zone diameters from the disc test with MIC (minimal inhibitory concentration) values for rifampin.

HOW SUPPLIED

Capsules (opaque red), imprinted "RIFAMATE" on both ends of the capsule, containing 300 mg rifampin and 150 mg isoniazid; bottles of 60 (NDC 0068-0509-60).

Storage: Keep tightly closed. Store in a dry place. Avoid excessive heat.

Manufactured for:

sanofi-aventis U.S. LLC

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